The FDA Phase 1 GMP Guidance

CGMPS By The Sea
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Presentation Overview

- Current Situation
  - Regulatory Basis
  - CGMP in Clinical Investigations
- Proposed Approach – Rule & Guidance
  - General Principles
  - Consideration for Phase 1 Studies
  - Special Production Considerations
- Considerations for Late Phase Clinical Studies

FDA is currently evaluating submitted docket comment
to proposed rule and guidance
Comments reflect the current drafts and may change

Regulatory Basis

- All drugs and biologics including investigational new drugs are required to be manufactured in accordance with CGMPs
  - if not, considered adulterated [501(a)(2)(B) Food, Drug and Cosmetic Act]
- Current Good Manufacturing Practices for Finished Pharmaceuticals Regulations [21 CFR 210, 211] [1978]
- No specific regulations for API production
  - (Q7A GMP Guidance For Active Pharmaceutical Ingredients [Adopted by FDA, September 2001])

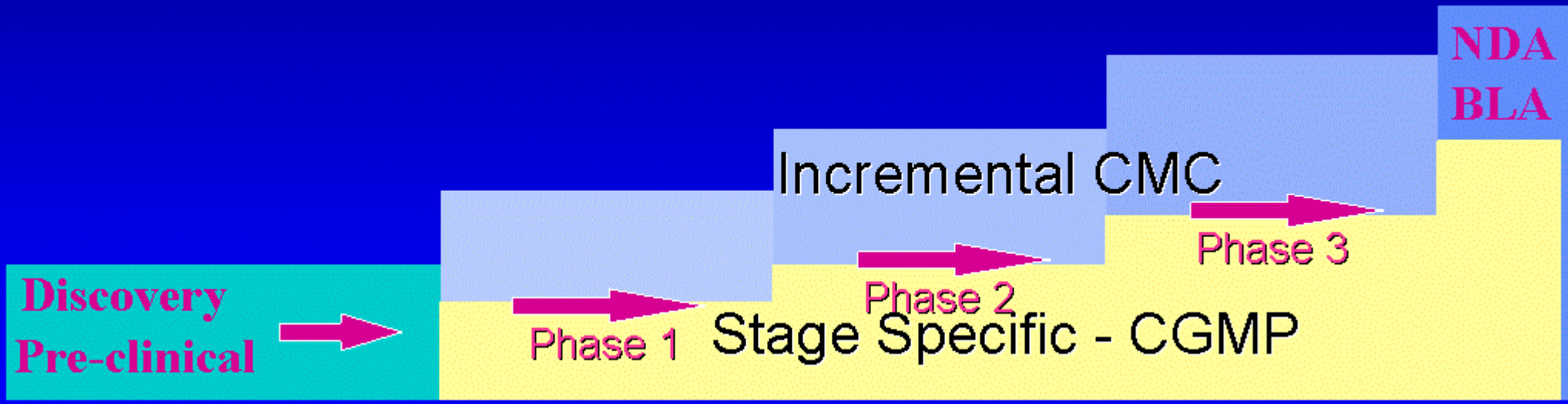
Regulatory Basis

- Compliance with CGMP regulation (i.e., 21CFR 210, 211) are applicable for approved drugs and investigational new drugs for administration to humans or animals
  - "The Commissioner finds that, as stated in 211.1, **these CGMP regulations** apply to the preparation of any drug product for administration to humans or animals, **including those still in investigational stages.**" [Response to comment #49, Preamble 1978 CGMP rule]
  - "… the process by which a drug product is manufactured in the development phase **be well documented and controlled…**" [Response to comment #49, Preamble 1978 CGMP rule]

Investigational Studies & 21 CFR 211's

- Not always possibly to fully comply with CGMP regulations (i.e., 21 CFR 211)
- Some CGMP regulations designed for repetitive, commercial manufacture of an approved product
  - Defined product quality attributes; uses an established manufacturing process
- Types and extent of some controls may differ – due to stage of development between investigational and commercial manufacturing, as well as phases of investigational clinical study
  - The Commissioner is considering proposing additional CGMP regulations specifically designed to cover drugs in research stage [Response to comment #49, Preamble 1978 CGMP rule]
- However, CGMP principles are clearly applicable to manufacture of investigational new drug products

CGMP in Clinical Investigation



CGMP & Product Development

SAFETY INFORMATION

Source characterization

Raw materials qual

DS/DP Characterization

Testing/Qualification/ Clearance of impurities, contaminants

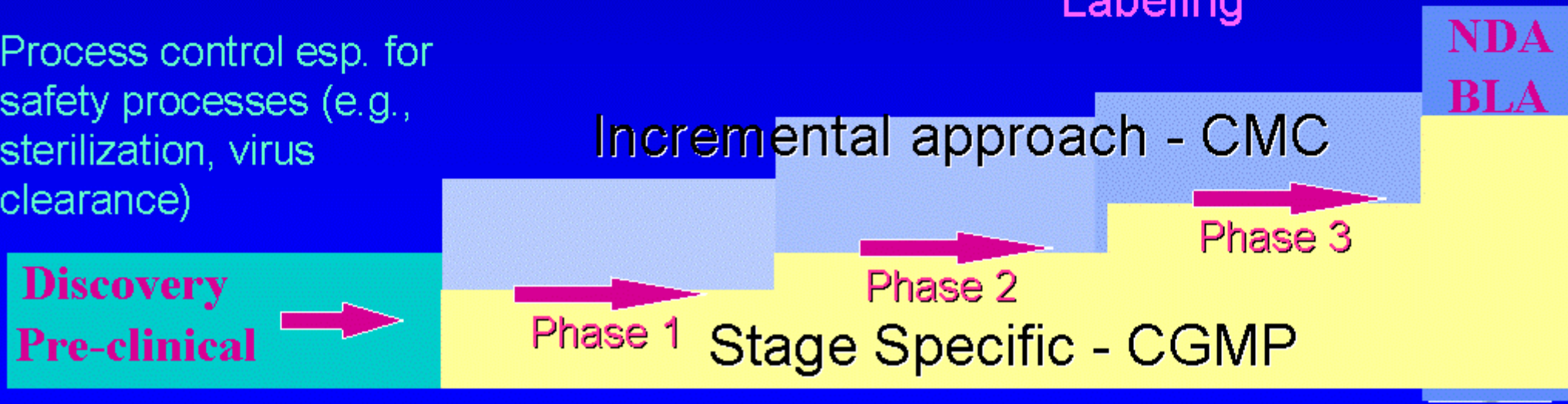
Process control esp. for safety processes (e.g., sterilization, virus clearance)

DEVELOPMENT ACTIVITIES

DS & DP Characterization
Formulation Development
Raw Material/ Component characterization
Assay Development/ Validation
Specification Development
Stability
Manufacturing Process Control & Validation

CGMP

Personnel
Quality Control
Facilities & Equipment
Laboratory Control
Component Control
Production Control
Distribution & Records
Labeling



Existing FDA CGMP Guidance For Investigational Studies

- FDA Guidance aimed at fostering compliance with CGMP, however few directly address issue related to CGMP in clinical investigation
  - "FDA Guideline on the Preparation of Investigational New Drug Products (Human and Animal)" 1991
  - Section 19, Q7A GMP Guidance For Active Pharmaceutical Ingredients [FDA adopted September 2001]

Approach

- Why Now ?
- Why CGMPS for Phase 1?
- Why this Approach ?

What Does FDA Hope to Achieve By This Approach?

- Provide some clarity on approach and expectations
- Help assure safe investigational products
- Facilitate product development

What has changed in the regulation of CGMPS for Phase 1 Investigational New Drugs?

Overall Approach

- Some controls and extent of controls differ between investigational and commercial manufacturing, as well as phases of investigational clinical study
  - May need to have more stringent controls during development in some areas and circumstances
- FDA's intent to implement an incremental approach to CGMP compliance for clinical investigational products

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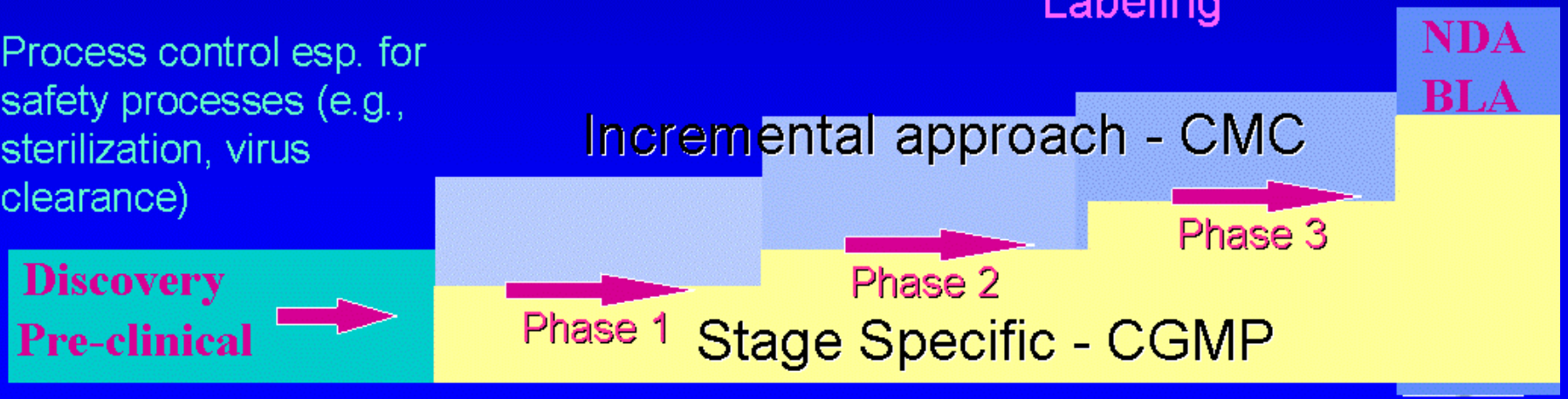

Potential Regulatory Actions

- Review Activity
  - **"Every IND must contain, among other things, a section on CMC that describes the composition, manufacture, and control of the IND 21 CFR 312.12(a)(7)."**
  - **"Under IND authority, FDA had the option to place an IND on clinical hold if the study subjects would be exposed to an unreasonable and significant risk or if the IND does not contain sufficient information to assess the risks to subjects, 21 CFR 312.42."**

Potential Regulatory Actions

- "Even if exempted from the requirements of parts 210/ 211, investigational drugs remain subject to the statutory requirement the deems a drug adulterated, FD&C Act 351(a)(2)(B)."

- **"Even though the FDA is exempting Phase 1 drug products from compliance with the specific requirements of the CGMP regulations, the agency retains the ability to take appropriate actions to address manufacturing issues.**

- **Inspectional Activity**
  - **Manufacturing and testing sites are subject to inspection**
  - **No formal inspection prerequisite requirement for sites manufacturing clinical investigational drugs**

Proposed and Direct Final Rule

- **On January 17, 2006, FDA published a proposed rule and a direct final rule in the Federal Register to amend current good manufacturing practice (CGMP) regulations for human drugs, including biological products, to exempt most investigational "Phase 1" drugs from complying with the CGMP regulation (21 CFR 210/211).**
  - **http://www.fda.gov/ohrms/dockets/98fr/06-353.htm**
- **DFR withdrawn on May 2nd**

Proposed and Direct Final Rule

- 2. Section 210.2 is amended by adding paragraph (c) to read as follows:
- **§ 210.2 Applicability of current good manufacturing practice regulations.**
  - * * * * *
- **(c) An investigational drug for use in a Phase 1 study, as defined in§ 312.21(a) of this chapter, is subject to the statutory requirements set forth at 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter.**

Proposed and Direct Final Rule

- "However, this exemption does not apply to an investigational drug for use in a Phase 1 study once the investigational drug has been made available for use by or for the sponsor in a Phase 2 or Phase 3 study, as defined in § 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed."
- "If the investigational drug has been made available in a Phase 2 or 3 study or the drug has been lawfully marketed, the drug for use in the Phase 1 study must comply with part 211."

Companion Draft Guidance

- At the same time, FDA published a draft guidance
  - *"INDs – Approaches to Complying with CGMP During Phase 1"*
  - to provide guidance for "recommendations on approaches to statutory compliance" for the manufacture of Phase 1 material
- http://www.fda.gov/cber/gdlns/indcgmp.pdf

Draft Guidance: Development

- Compatible and complementary to IND regulations
- Intended to serve as a companion to other guidance describing CMC information submitted and reviewed in IND applications
- Intended to be one reference for CGMP - guidance focusing on approaches

Draft Guidance: Scope

- Applies to:
  - Investigational new drug and biological drug products used during phase 1 development
    - Investigational recombinant and non-recombinant therapeutic products, vaccine, gene therapy, allergenic, plasma derived, and somatic cellular therapy products as well as in vivo diagnostics
    - Exploratory INDs
- Applies to
  - Manufacturers including
    - specialized service providers (contractors, testing facilities)
    - Commercial and Sponsor-manufacturer
    - IND Sponsor
  - Drug Substance and Drug Products

Draft Guidance: Development Principles

- Assure safe investigational products
  - Assure quality of investigational product
- Ability to reproduce investigational product, as needed
- Assure consistent quality of investigational product
  - Within a trial
  - Between trials
  - Throughout development to commercial manufacture

Achieving CGMP Compliance

- Effective quality control standards for Phase 1
  - Well defined written procedures
  - Adequately controlled equipment
  - Accurate and consistent recording of all data (manufacturing and testing)
- Implement CGMP consistent with good scientific methodology, product development and quality principles

Approaches & Challenges

- Utilize (develop) control measures specifically tailored to the product, manufacturing process and facility
- How to determine CGMPs that are appropriate for my process, product and stage of clinical trial?
- Utilize comprehensive and systematic assessment
  - document your rationale
  - apply safeguards before, and during manufacture
- CGMP are written to allow flexibility, however, this has potential for subjective interpretation by producer & investigator - Alternative ???
- CGMP are minimum requirements/ expectations

Achieving CGMP Compliance

- Utilize Technology & Resources
- Facilitate
  - CGMP compliance
  - Streamline Product development
- For example, consider utilizing
  - Use disposable equipment and process aids
  - Prepackaged WFI & sterilized containers
  - Closed process equipment
  - Contract or shared production & testing facilities

Achieving CGMP Compliance

- Implement controls - shown to be both feasible and valuable in assuring drug quality

Not an excuse for inadequate controls !

- Specific product and manufacturing process may impact ability to comply – decide and document
- Not possible to follow comply with CGMP
  - Include rationale for approaches followed in records for investigational product
  - Include reasons not follow obvious recommendations

CGMP Inspection

- Personnel
- Quality Control
- Facilities
- Equipment
- Laboratory Control
- Component Control
- Production Control
- Distribution
- Records
- Labeling

Quality Control

- **Quality Control Function**
  - QA, QC, Quality Systems ???
  - Implementation is an organizational decision
- Written plan – roles and responsibilities
  - Review and release components
  - Review and approval of production procedures, testing procedures & acceptance criteria
  - Release or reject each batch upon cumulative review
  - Investigate errors and initiate corrective action
- Responsibilities are performed independently from production
- Appropriately trained individual's – sufficient to perform QC function

Facilities

- Dependent upon manufacturing operation and product
- Adequate and appropriate - HVAC, light, water, plumbing, space etc.
- Adequate work areas for intended tasks
- Water of appropriate source and quality
- Adequate air handling to prevent contamination and cross-contamination
- Procedural controls to avoid contamination and mix-ups

Equipment

- Appropriate for intended function
- Adequately controlled
  - Qualified?
- Properly maintained, calibrated, cleaned and sanitized following written procedures and at appropriate intervals
- Should not contaminate or be reactive additive or absorptive with product
- Identified and documented in production records

Components

- Written procedures describing handling, and control of components
- Establish specified attributes & acceptance criteria (AC)
  - (attributes & AC not always possible)
- Review of documentation (COA) to ensure conformance/ testing for incomplete documentation
- Consider limited testing
- Record relevant information – traceability!

Production and Documentation

- Production follow written procedures
- Record of manufacturing and testing data
  - components, equipment and procedures used
  - sufficient detail to allow for reproduction of product
- Records of changes in procedures and processes – rationale for change
- Records of microbiological control for sterile processed drugs

Laboratory

- Production tests (component, in-process, DS, DP)
  - Specified quality attributes monitored – appropriate acceptance criteria applied (e.g., known safety-related and other tests as appropriate)
  - Analytical procedures
    - scientifically sound (e.g., specificity, sensitivity, accuracy)
    - reliable & suitable for intended purpose
  - Tests conducted using written procedures under controlled conditions
  - Periodic calibration and maintenance of laboratory equipment
    - Consider systems suitability

Laboratory

- Retain representative sample for additional release testing –
  - Recommended – 2X quantity needed for release testing
- No formal expiration date - initiate stability study to support use throughout clinical trial

Packaging, Labeling

- Protective packaging - commensurate with risk to product
- Written procedures to prevent mix-ups
- Variable studies – (e.g., placebo, blinded, multiple strengths)
- Appropriate procedures (e.g., product segregation, label reconciliation, confirmatory identity testing, operation verification by a second person, QC review)

Special Production

- Sterile/ Aseptic Processing
- Multiproduct Facilities
- Biological/ Biotechnological Products
- Other Situations

Sterile/ Aseptic Processing

- Primary area of assuring safety for some products
- Can be challenging to control and assure in early investigational phases
  - Appropriate training
  - Aseptic manipulation conducted under appropriate conditions (e.g., Class 100 conditions - laminar flow hood)
  - Appropriate simulations (e.g., media fills)
  - Monitoring
  - Highly controlled equipment “Qualified” provide a high degree of assurance that process works
  - Document and follow all procedures intended to maintain the sterility of the components, in-process materials, components and final product

Multiproduct

- Multi-product
  - Generally, only one product manufactured in an area/ room at a time
  - Same area/ room may be used for multiple purposes, if:
    - Appropriate design & procedural controls allow for orderly handling of materials & equipment – prevent contamination/ cross contamination, mix-ups
    - Effective cleaning and change over procedures
- Multi-product aspects – potential impact on other product
  - Have you considered unknowns?
  - **Don’t place existing systems, process and facilities at risk**

Biotechnology and Biological Products

- Appropriate equipment control in production needed to assure safety related function (e.g., viral clearance, viral toxin inactivation, pasteurization) will perform as intended
  - Accompanying testing for safety related functions
- Difficulties to distinguish changes in quality attributes or predict impact of observed changes on safety
- “Comparability”
  - Comprehensive documentation
  - Control and documentation
  - Sufficient retains – appropriately stored

Multiple Batches

- Produces of multiple batches (e.g., therapeutic vaccines, cell therapies)
  - Consistency among batches is important
  - Accelerated accumulation of data than typical manufacture
  - Periodic review and modification to control procedures and production operations – especially related to safety

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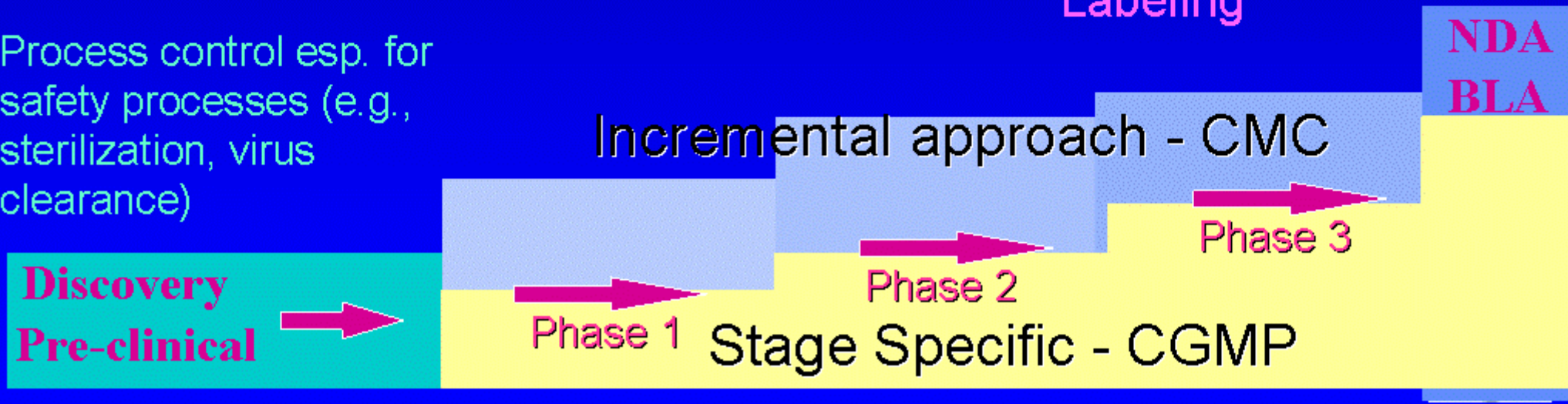

Considerations for Later Phase Clinical Studies

- Overall, probably not introducing new areas of CGMPs
  - Refining control or greater degree of control in some areas
- CGMP reflect and are consistent with good product development
  - Continue to assure safe products – quality perspective
  - Implement controls that reflect accumulated product and process knowledge and experience
  - Provide greater assurance in linking product quality to commercial manufacture

Considerations for Later Phase Clinical Studies

- Reflective of some aspects of commercial manufacture
  - Scale
  - Number of lots produced
  - Evolution in process, analytical methods
- Different facilities (e.g., pilot plants, commercial manufacturing)
  - Integrate into existing systems & CGMP
  - Multiproduct aspects – potential impact on other products
    - Don’t place existing systems, process and facilities at risk

- FDA Investigational CGMP Working Group
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